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SNELL & WILMER L. L. P.
ONE ARIZONA CENTER
400 EAST VAN BUREN
PHOENIX, AZ 85004-0001

EXAMINER	
COUNTS, GARY W	
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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte
RANDALL W. NELSON,
PETER WILLIAMS, and JENNIFER REEVE KRONE

Appeal 2007-3937
Application 09/808,314
Technology Center 1600

Decided: January 24, 2008

Before DEMETRA J. MILLS, NANCY J. LINCK, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 31-33, 35-40, 42, 44-46, and 48. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claimed invention is directed to a method of quantifying an analyte present in a specimen. The method comprises three steps: a) combining the specimen with an internal reference species (IRS); b) capturing the analyte and IRS using an affinity reagent (such as an antibody); and c) quantifying the amount of analyte using "only single dimension mass spectrometric analysis to resolve distinct signals for the analyte and said IRS." A specimen can be any material which is the focus of the mass spectrometric immunoassay, including of biological or non-biological origin (Specification 17).

Claims 1-14, 20-33, 35-40, 42, 44-46, and 48 are pending (Appeal Br.[1] 2). Claims 1-14 and 20-30 are withdrawn from consideration; claims 31-33, 35-40, 42, 44-46, and 48 are appealed (*id.*).

The following rejections have been presented by the Examiner for our review:

1) Claims 31-33, 35, and 36 under 35 U.S.C. § 103(a) as obvious over Papac (*Anal. Chem.*, 66: 2609-2613, 1994) in view of Gaskell (*Steroids*, 55: 458-462, 1990) (Answer 4);

2) Claims 37-40 and 42 under 35 U.S.C. § 103(a) as obvious over Papac in view of Gaskell as applied to claims 31-33, 35, and 36, and further in view of Chiabrando (*J. Chromatography*, 495: 1-11, 1989) (Answer 6);

3) Claims 44-46 and 48 under 35 U.S.C. § 103(a) as obvious over Papac in view of Gaskell and Chiabrando as applied to claims 31-33, 35-40, and 42, and further in view of Merren (U.S. Pat. No. 3,770,337, Nov. 6, 1973) (Answer 6); and

[1] "Appeal Br." refers to "Appellant's Second Substitute Brief Pursuant to 37 C.F.R. § 41.37" filed Jan. 2, 2007.

4) Claims 31 and 37 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 31-50 of copending Application Serial No. 09/024,988 (Answer 7). This is a provisional rejection since the conflicting claims have not been patented (Answer 8).

We select claim 31 a representative of the appealed subject matter. Claim 31 reads as follows:

> A method for quantifying the relative amount of one or more analytes present in a specimen, comprising the steps of:
>
> a. combining said specimen with a known amount of internal reference species (IRS) if the specimen does not already contain one;
>
> b. capturing and isolating at least one of the one or more analytes and said IRS, wherein said capturing and isolating step comprises a substep of combining said IRS containing specimen with an affinity reagent;
>
> c. quantifying the at least one of the one or more analytes in which said quantifying step comprises using only single dimension mass spectrometric analysis to resolve distinct signals for the analyte and said IRS to determine the amount of the captured analytes relative to the IRS.

ISSUE ON APPEAL

The Examiner contends that Papac teaches a mass spectrometric method of identifying analytes that involves the capture and isolation of the analyte with an affinity reagent as required by step b. of claim 31, but does not describe quantifying the analyte using an internal reference species as required by the claim (Answer 4-5). However, the Examiner contends that this step is taught by Gaskell and that it would have been obvious to have modified Papac's method with Gaskell's teachings to have made the claimed invention (Answer 5).

Appellants contend that it would not have been obvious to persons of ordinary skill in the art to have combined Papac and Gaskell to have made the claimed invention (App. Br. 13).

We frame the issue in this appeal as follows: whether persons of ordinary skill in the art would have had reason to combine the prior art teachings of Papac and Gaskell to have made the claimed invention.

DISCUSSION

Obviousness of claims 31-33, 35, and 36

Claims 31-33, 35, and 36 stand rejected under 35 U.S.C. § 103(a) as obvious over Papac in view of Gaskell.

"[T]he Examiner bears the initial burden, on review of the prior art . . , of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Scope and contents of the prior art

In making an obvious determination, the Examiner must first identity the scope and contents of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Thus, we first turn to the prior art. The following numbered findings of fact ("FF") summarize the prior art relied upon by the Examiner in setting forth the basis of the rejection (Answer 4-5):

The Papac publication

1. Papac describes a method for the mass spectral detection of analytes separated by immunoaffinity chromatography (Papac, Abstract).

2. A monoclonal antibody to cytochrome c (mAb E8) was attached to agarose beads and used as an affinity column (Papac, at 2611, cols. 1-2) to purify cytochrome c.

3. A solution comprising cytochrome c was passed through the column (Papac, at 2611, col. 2).

4. An aliquot of the column comprising bound cytochrome c was analyzed by MALDI/TOF mass spectroscopy (*id.*).

5. "The only species observed is cytochrome c with" a molecular weight of 12,448 Da (*id.*; Fig. 2 on 2612).

The Gaskell publication

6. Gaskell describes fast atom bombardment/tandem mass spectroscopy (FAB/MS or liquid SIMS) to quantify an analyte which is steroid conjugate (Gaskell, at p. 458 and p. 460, col. 1).

7. An isotopically labeled internal standard is added to a serum sample which comprises the analyte (Gaskell, p. 460, col. 1; Answer 5).

8. The internal standard of Gaskell is the same element as the "internal reference species (IRS)" of claim 31.

9. The sample is added to an affinity column which contains Sepharose coupled to an antiserum specific for the analyte and standard (*id.*).

10. After binding the analyte to the Sepharose-coupled antiserum, the analyte and was eluted from the column and subjected to mass spectroscopic analysis (Gaskell, at p. 460-61).

11. "Gaskell discloses that for quantification of the analyte, the analyte and internal standard are compared to a standard curve (p. 460). Gaskell discloses that the standard curve was obtained by analyses of standard mixtures of the analyte" and the internal standard (Answer 5).

12. The "most rigorous quantitative analyses using liquid SIMS require the use of isotopically labeled internal standards, a conclusion that parallels much previous experience in the application of GC/MS to quantitative analyses" (Gaskell, at p. 459, col. 2; *see also* Answer 5).

Differences between the prior art and the claimed invention

Once the scope and contents of the prior art has been determined, the next step is to identify the differences between the prior art and the claimed invention. *Graham*, 383 U.S. at 17. The following numbered findings of fact are pertinent to this issue.

13. Each of Papac and Gaskell describe immunopurification of an analyte prior to its detection by mass spectroscopy (FF 1-4, 9, 10; Papac, at pp. 2611-12; Gaskell, at pp. 460-61) which satisfies the limitation of claim 31 of "b. capturing and isolating at least one" analyte.

14. Papac does not describe "a. combining" a specimen "with a known amount of an internal reference species" of claim 31 (Answer 5).

15. Papac does not describe "c. quantifying" the analyte "using only single dimension mass spectrometric analysis to resolve distinct signals for the analyte and said IRS to determine the amount of the captured analytes relative to the IRS" as recited in claim 31.

16. However, Gaskell describes immunopurifying an analyte and an internal standard (FF 7-9; Gaskell, at p. 460-61) as recited in step b. of claim 31.

17. Gaskell also describes quantifying the amount of analyte using the signals from the analyte and the internal standard in mass spectroscopy (FF 11-12; Gaskell, at pp. 459-60; Answer 5), but not "using only a single dimension mass spectrometric analysis" as recited in step c. of claim 31.

Reason to combine the prior art

Once the differences between the prior art and the claimed invention have been ascertained, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

In this case, the Examiner contends that it

> would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate an internal standard and affinity reagents and also develop a standard curve for quantification analyses, as taught by Gaskell, into the method of Papac . . . [b]ecause Gaskell teaches that the addition of an internal standard would provide for precise and accurate data and for the quantification of an analyte of interest.

(Answer 5.)

In our opinion, the Examiner has provided sufficient evidence and reason to establish prima facie obviousness of the claimed invention. The following findings of fact are relevant to this conclusion:

18. As found by the Examiner, Gaskell explicitly teaches that an internal standard is used to achieve "rigorous quantitative analyses" of an analyte in mass spectroscopy (FF 11-12; Gaskell, pp. 459-60; Answer 5).

19. An internal standard is utilized in not only FAB/MS, but also in GC/MS (FF 12; Gaskell, at p. 459, col. 2; Answer 5).

20. Based on Gaskell's teachings (FF 18, 19), persons of ordinary skill in the art would have known that an internal standard is routinely utilized in mass spectroscopy to determine the quantity of an analyte of interest in a sample.

21. Thus, persons of ordinary skill in the art would have had reason to have modified Papac's method by combining a sample with a known amount of an internal standard as taught by Gaskell to "provide for precise and accurate data and for the quantification of an analyte of interest" (Answer 5; FF 11, 12) – meeting the steps of claim 31 which are deficient from Papac (FF 14, 15).

If "a technique has been used to improve one device, and a person of ordinary skill would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 127 S. Ct. at 1740.

22. Here, internal standards had been utilized in certain mass spectroscopic methods to quantify the presence of an analyte in a sample (FF 11-12; Gaskell, at pp. 459-60; Answer 5).

23. Therefore, ordinary skilled artisans would have recognized its benefit to improve analyte quantification in other mass spectroscopic methods (FF 18-20).

Appellants argue that "the Gaskell reference actually teaches away from Appellant's claimed invention with respect to Appellant's quantifying step contained in its claims because Gaskell uses tandem MS for quantification" and not "single dimension mass spectroscopy" as in the claimed invention (Reply Br. 3; *see also* Appeal Br. 13).

We do not agree. A reference teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. . . . [I]n general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). In this case, Appellants have not pointed to any disclosure in Gaskell which would have led a person of ordinary skill not to use an internal standard in Papac's method. Nor have Appellants provided any technical reason as to why an internal standard would not work in MALDI/TOF spectroscopy – the particular spectroscopic method utilized by Papac. Thus, we see no error in the Examiner's findings or his conclusion.

Appellants also contend that "unlike Applicants' claimed invention, the Papac reference analyzes a predetermined analyte and not the identification and amount of analyte present in a biological or physiological specimen" (App. Br. 12).

We do not find this argument persuasive. Claim 31 is directed to a method of "quantifying the relative amount of one or more analytes present in a specimen." There is no language in the claim which excludes the analyte from being predetermined nor that requires the analyte to be present

in "a biological or physiological sample"[2] as argued by Appellants. Thus, Appellants are attempting to distinguish the claimed invention over prior art by limitations which are not recited in the claims.

Appellants also state that the "Papac reference fails to disclose any quantification whatsoever of the analyte" (App. Br. 12). They refer to Papac's discussion on page 2611 of Figure 1 in which an antibody was captured by affinity chromatography and then analyzed by MALDI/TOF mass spectroscopy (*id.*).

We are not persuaded by this argument. Appellants have pointed to the wrong disclosure in Papac. The Examiner relied upon Papac's teaching as illustrated in Figure 2 on page 2612 in which cytochrome c was analyzed by MALDI/TOF mass spectroscopy (FF 2-5; Answer 9).

For the foregoing reasons, we affirm the rejection of claim 31. Claims 32, 33, 35, and 36 fall with claim 31 because separate reasons for their patentability were not presented. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Obviousness of claims 37-40, 42, 44-46, and 48

Claims 37-40 and 42 stand rejected under 35 U.S.C. § 103(a) as obvious over Papac in view of Gaskell as applied to claims 31-33, 35, and 36, and further in view of Chiabrando.

Claims 44-46 and 48 stand rejected under 35 U.S.C. § 103(a) as obvious over Papac in view of Gaskell as applied to claims 31-33, 35, and 36, and further in view of Merren.

Appellants argue that the Chiabrando does not disclose the use of single dimension mass spectroscopy to analyze and quantify an analyte

[2] The Specification states that "the specimen may be non-biological in origin" (Specification 17).

(App. Br. 14) and that Merren fails to single dimension mass spectroscopic analysis of an analyte and an internal reference species (App. Br. 15). As pointed out by the Examiner, these aspects are suggested by the combination of Papac and Gaskell (see Answer 12-13). Thus, Appellants have not provided separate arguments for the patentability of claims 37-40, 42, 44-46, and 48, but instead rely on the same arguments as for claim 31 (*see also* Reply Br. 4-5). Consequently, since we see no defect in the Examiner's reasoning with respect to claim 31, we affirm the rejections of 37-40, 42, 44-46, and 48 for the same reasons as set forth above for claim 31.

Provisional obviousness-type double patenting rejection

Claims 31 and 37 stand provisionally rejected under the judicially created obviousness-type double-patenting over claims 31-50 of copending U.S. Application Serial No. 09/024,988.

Appellants have not addressed the merits of this rejection. Consequently, we summarily affirm it. We note that the copending application has been appealed (*see* Appeal Brief filed Mar. 19, 2007 in U.S. Application Serial No. 09/024,988).

CONCLUSION

We affirm the obviousness rejections of claims 31-33, 35-40, 42, 44-46, and 48 over prior art and the provisional obviousness-type double patenting rejection of claims 31 and 37 over copending Application Serial No. 09/024,988.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

Ssc:

SNELL & WILMER L.L.P.
ONE ARIZONA CENTER
400 EAST VAN BUREN
PHOENIX, AZ 85004-0001